



## **Generic pMDI Product Development: Key Considerations**

### **Reducing Risks, Mitigating Failure, and Driving Timelines in a Competitive Market**

**White Paper / April 2013**

#### **Rationale and Introduction**

Currently there are no generic Asthma/COPD inhalers available in the United States. This includes both categories of standard asthma treatment: rescue medication for quick relief and controller medications for long term prevention. The average cost of the above inhaler medicines ranges from \$35 - \$300, rendering the treatment expensive for both insured and uninsured consumers. At the same time, the opportunity is ripe for generic companies racing to be the first to market and to grab a slice of the 5 billion dollar pie.

As many pressurized metered dose inhalers (pMDIs) approach patent expiration, and with the lack of a guidance document from the US Food and Drug Administration (FDA), generic companies are reluctant to invest in product development which ultimately may not be acceptable to the Agency. In this white paper, Next Breath highlights key considerations and addresses strategies that are believed to reduce risk and ultimately speed up the process for getting a generic pMDI product to the US market. This white paper will focus on the key considerations and a stepwise approach that we believe are critical in managing the complexities and unknowns around the development of generic pMDIs.

#### **API Selection and Excipients**

Selecting the proper active pharmaceutical ingredient (API) and excipients is a key consideration that must be made very early in the Abbreviated New Drug Application (ANDA) process. Ensuring that the selected API and excipients are comparable to the marketed Reference Listed Drug Product (RLD) is fundamental to achieving *in vitro* bioequivalence (IVBE). A generic formulation must be qualitatively and quantitatively (Q and Q) similar to the RLD, which means that the API dose is identical to the label claim of RLD and the excipient levels in the generic formulation are  $\pm 5\%$  of the RLD concentrations. During API/excipients selection, ANDA applicants should source the API from at least three suppliers that are registered with the FDA and have a proven track record of supplying APIs to products that are currently approved in regulated markets.

Determination of the correct particle size of the API is critical, especially for suspension pMDIs and will affect IVBE outcomes. The applicant should also request the manufacturer of the drug substance to provide pertinent chemistry, manufacturing, and controls information. Insuring that there is a DMF available (DMF; 21CFR 414.20) for the formulation components is an important step in the selection process.

In addition, a Certificate of Analysis (C of A) should be requested to substantiate that the batch meets all tests and specifications. Where applicable, the API and excipients must adhere to USP monograph/National Formulary guidelines. Following evaluation of the documentation from the API vendor, ANDA applicants should perform a comprehensive screening study of the selected API at the applicant's facility. The goal of this screening study is to confirm that the results generated on site match the vendor's C of As. This confirmation step may appear trivial or redundant on the surface, but it can and has been a source of many delays, surprises, and wasted resources when the vendor's API specification cannot be reproduced when tested independently.

### **Container and Closure System**

Unlike most dosage forms that contain formulations in simple packaging systems, pMDIs have unique features; a pMDI consists of a container, a valve, an actuator (mouthpiece), and the formulation with a highly volatile propellant packaged under pressure (Figure 1). The manufacturing process, packaging, and dispensing components play as much of a critical role in the overall success of the product as the formulation itself. These components collectively constitute the drug product that delivers the drug substance in the desired physical form to the biological target (1). Therefore, all components of the pMDI design warrant a thorough consideration regarding chemistry, manufacturing, and controls and *in vitro* performance. These complex and subtle interactions between the drug substance, excipients, container closure system, and simulated patient use conditions can all have a significant impact on the *in vitro* BE of the Test product to the RLD of the marketed pMDI.



Figure 1-pMDI using Aptar Landmark<sup>®</sup> Dose Indicator

Following a thorough patent examination of the RLD of interest (these are generally available in the FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book), ANDA applicants should engage device vendors early in the development process. This is particularly critical for selecting the metering valve and actuator components given their impact on the aerosolization and particle size distribution of the drug product. ANDA applicants should be prepared to reference supporting Drug Master Files (DMF) of the packaging system from the manufacturer and provide

schematic drawings, full descriptions, chemical compositions, regulatory status, and in-house tests and specifications for acceptance or rejection of the aerosol can, actuator, actuator dust cap, and metering valve [21 CFR 211(Subpart E)] (2).

The Division of Bioequivalence recommends that the ingredients used in the formulation should be qualitatively identical and quantitatively as close as possible to those of the reference product (3). The valve and actuator of the RLD product may be proprietary to the innovator and, as a result, unavailable to ANDA applicants. The Division therefore recommends that the generic firm assure functional equivalence of Test and RLD products through both *in vitro* and *in vivo* testing (1). In the early engagement process with device vendors, ANDA applicants should request vendors (some of which also supply the Innovator) to provide alternative pMDI components that are comparable to the RLD device. They should also request data that supports the selection of the alternative Test components. Vendors that understand this paradigm have begun to generate preliminary data using their proposed generic alternatives to the RLD and may be able to provide them to ANDA applicants upon request. Next Breath and Aptar (vendor of approved pMDI valves) are preparing a data package comparing RLD components to alternative proposed generic components to facilitate container closure selection.

### **In vitro BE Testing Requirements**

ANDA applications are required to demonstrate that the proposed generic product is pharmaceutically equivalent [21 CFR 320.1 (c)] as well as bioequivalent [21 CFR 320.1 (e)] to the RLD (2). One of the key aspects to approval of generic drug products in the US, including locally acting orally inhaled drug products (OIDPs), is the demonstration of *in vitro* and *in vivo* BE. The current US FDA approach for establishing BE of OIDPs is based on an aggregate weight of evidence (4). It utilizes *in vitro* studies to demonstrate equivalent *in vitro* product performance, pharmacokinetic (PK) studies to establish equivalent systemic drug exposure, and pharmacodynamic (PD) studies to support equivalence in local drug delivery (2). It is important for ANDA applicants to ensure that the submission is aligned with the expectations of international regulatory agencies outside of the US. Different regulatory agencies have different recommendations for achieving BE. Figure 2 illustrates the different approaches between the European Medicine Agency (EMA) and the FDA to an ANDA application for OIDPs (2).

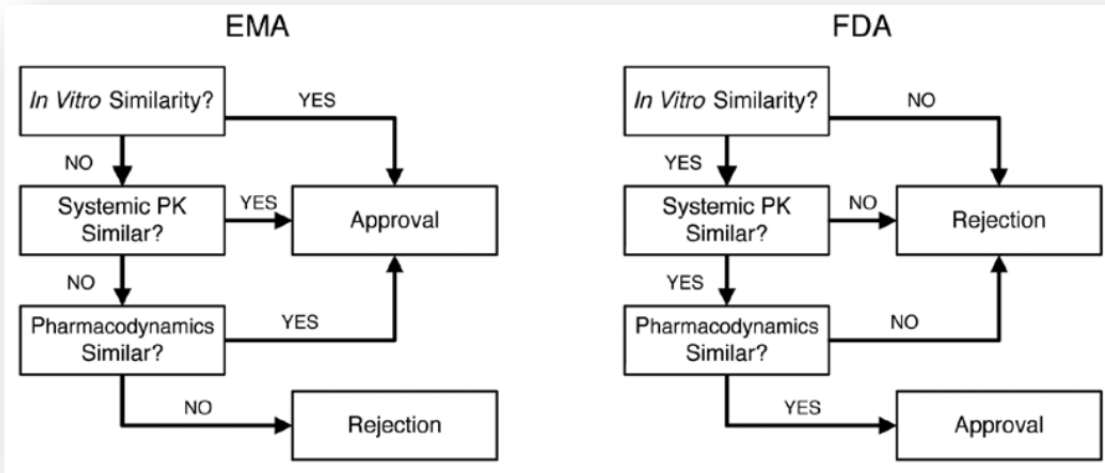


Figure 2 Comparison of EMA and FDA decision trees for assessing IVBE of OIDs (2).  
 EMA: European Medicine Agency (equivalent of the FDA) oversees most of the member states of the European Union.

The FDA approves pMDIs as specific combinations of formulation and device. Each of the major components, including specific formulation (propellant and concentrate), and container and closure system (valve, actuator, and container) contributes to the biopharmaceutical performance of the product. In the absence of specific guidance, ANDA applicants must rely on the present thinking on this topic spanning review of literature from the chlorofluorocarbon propellants (CFC) switch to the hydrofluoroalkane (HFA) in the early 1990s, the present FDA workshops and conference presentations and, most recently, Respiratory Drug Delivery to the Lungs (RDD 2012) and Drug Delivery to the Lungs (DDL 2012) to construct a robust regulatory package for pMDI ANDA applications. Demonstration of equivalence in the emitted dose (ED) and aerodynamic particle size distribution (APSD) constitute the key *in vitro* components used to support BE for generic pMDIs.

These *in vitro* performance attributes estimate the total and regional deposition of drug substance in the lung and demonstrate quality attributes between Tests and RLDs and are therefore central to demonstrating IVBE. In addition, ANDA applicants are required to perform long term stability (Test products only) and comprehensive *in vitro* testing as presented in the CMC guidance for pMDIs and DPIs (5). For example, applicants should provide data on Test products for profiling of actuations near canister exhaustion for MDIs, the effect of resting time, the effect of storage on the

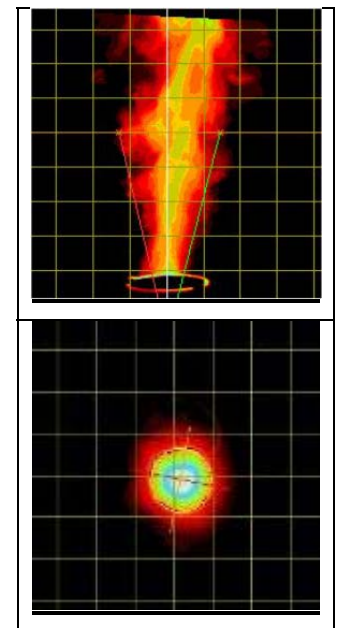


Figure 3-4 pMDI plume Geometry and Spray Pattern (Proveris SprayView®)

particle size distribution (in case of suspension MDIs), cleaning instructions, etc.(complete list is available in the CMC guidance). ANDA applicants should also be prepared to provide statistical analysis. The FDA has recommended using the population bioequivalence analysis based on its 2001 guidance document comparing key data parameters from Emitted Dose (ED) and Aerosol Particle Size Distribution (APSD) studies (6). In addition, Next Breath recommends the inclusion of spray pattern, plume geometry, and prime/reprime in the IVBE and PBE activities. Images of spray pattern and plume of geometry of a typical pMDI is presented in Figure 3-4.

## **Conclusion**

The development and commercialization of inhaled pressurized products presents a number of unique challenges for ANDA applicants. The complexities in the pMDIs formulation, device design, performance, and absence of FDA guidance for pMDIs have created a high barrier to entry for new generic inhalers. In addition, Innovator companies are making it increasingly difficult for generics by introducing modifications to devices

and/or formulations to extend the lives of patents and to secure market exclusivity. For example, Teva introduced a dose counter to its already approved ProAir<sup>®</sup> following the Draft Guidance from FDA requiring all new pMDIs to include a dose counter/indicator (Figure 5). As a result, ANDA applicants must now include dose counters/indicators on their Test products to remain compliant with the sameness paradigm with the RLD.



Figure 5- Teva's ProAir<sup>®</sup> pMDI with dose counter

This white paper attempts to shed some light on the complexities and the very demanding process of a generic pMDI. It is our judgment that if ANDA applicants follow a stepwise approach focusing on the key considerations discussed above and move to the next phase only if a “Go, No Go” decision is achieved at each stage, the development process will become more manageable.

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Next Breath, a member of the AptarGroup, is a cGMP contract services organization for pharmaceutical, biotech and medical device companies that bring pulmonary, nasal, and ophthalmic drug products to market. Next Breath provides comprehensive solutions to the development processes from proof of concept to commercialization. Next Breath has led successful submissions for pulmonary and nasal drug products and devices in the US and international markets.